

The Influence of Potassium Administration and of Potassium Deprivation on Plasma Renin in Normal and Hypertensive Subjects

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ABSTRACT The effect of potassium administration and of dietary potassium deprivation on plasma renin activity and aldosterone excretion has been studied in 10 normal subjects and in 12 hypertensive patients maintained on a constant dietary regimen.

Potassium administration reduced plasma renin activity in 18 of 28 studies of both normal and hypertensive subjects. Suppression of renin often occurred despite sodium diuresis induced by potassium administration. The renin suppression was related to induced changes in plasma potassium concentration and urinary potassium excretion.

The failure of suppression of plasma renin in 10 studies could be accounted for by the smaller amounts of potassium administered to these subjects, together with a possibly overriding influence of an induced sodium diuresis.

In six studies potassium deprivation invariably increased plasma renin activity even though a tendency for sodium retention often accompanied this procedure.

The data indicate that both the suppression of plasma renin activity induced by potassium administration and the stimulation of renin activity which follows potassium depletion occur independently of associated changes in either aldosterone secretion or in sodium balance. However, the results do suggest that in various situations, the influence of potassium on plasma renin activity may be either amplified or preempted by changes in sodium balance.

These interactions between potassium and plasma renin could be mediated by an ill-defined extrarenal pathway. But the findings are more consistent with an

intrarenal action of potassium ions to modify renin release. Potassium might modify renin secretion directly by acting on the juxtaglomerular cells or by a change in its tubular reabsorption or secretion. The effects of potassium ions on renin secretion might also be mediated indirectly via an induced change in tubular sodium transport.

INTRODUCTION

Among the factors that have been shown to be involved in regulating renal renin release are the state of sodium balance (1), the amount of sodium delivered to the macula densa region of the distal tubule (2, 3), and a change in arterial blood pressure (4) or in the blood or extracellular fluid volumes (5).

An increase in plasma renin, by generating more of the circulating pressor hormone angiotensin II, operates as a major stimulus for eliciting aldosterone secretion by the adrenal cortex (6, 7). Potassium administration and changes in potassium balance also exert a potent influence on aldosterone secretion (8-13). Perfusion studies in animals have indicated that changes in plasma K^+ act directly on the adrenal cortex to increase aldosterone secretion (11). Thus, changes in sodium balance, by affecting renal renin secretion, and changes in plasma potassium, by a direct adrenal action, both operate to influence the activity of the renin-angiotensin-aldosterone system. This hormonal system therefore seems designed to be a regulator of sodium and potassium balance and of arterial blood pressure.

Other studies have shown that changes in potassium balance can affect plasma renin activity. Potassium administration in sodium-depleted human subjects caused a reduction in the previously high plasma renin (14).

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This suppressing effect of potassium could be an indirect consequence of potassium stimulation of aldosterone secretion or a more direct effect of potassium on renal renin secretion. The latter mechanism is supported by two reports which describe an acute reduction of plasma renin in dogs given potassium infusions (15, 16).

The present studies were designed to investigate further the possible relationship between changes in potassium balance and plasma renin activity in man. The results describe a reciprocal relationship between plasma renin and potassium balance. Potassium depletion was found to stimulate plasma renin activity. In addition, the suppressing influence of potassium administration on plasma renin was further characterized in both normal and hypertensive subjects. Both of these effects of potassium did not appear to be consequent to induced changes in aldosterone secretion, and they both occurred in the presence of changes in sodium balance which would be expected to have an opposite effect on plasma renin levels. When small amounts of potassium were given renin suppression was not observed. In this situation the overriding influence of induced changes in sodium balance often stimulated renin secretion. Taken altogether, these results suggest an intrarenal effect of potassium ions on renin secretion.

METHODS

Subject material. 34 studies employing constant dietary regimens were performed in 10 normal subjects and in 12 hypertensive patients on the metabolic ward of the Presbyterian Hospital. All subjects were fully informed of the nature and the objectives of the studies. The normal subjects were 10 male volunteers ranging in age from 20 to 44 yr old. A complete history and physical examination and routine laboratory tests revealed no evidence of any medical disorder in this group. Of the 12 hypertensive patients, 9 were classified as having essential hypertension and 3 as having renovascular hypertension. The 9 patients with essential hypertension comprised 3 males and 6 females, whose ages ranged from 26 to 61 yr old. In this group the blood pressure levels ranged from 150/100 to 260/140 mm Hg and the known duration of hypertension was 1–20 yr. In each case the diagnosis of essential hypertension was established by exclusion of all known causes of secondary hypertension. In addition to routine laboratory data the work-up included a timed sequence excretory urogram and a renal arteriogram. The 3 patients with renovascular hypertension were 2 females and 1 male. Their diagnoses were established by angiography and they were confirmed subsequently by a beneficial response to nephrectomy in all 3.

Experimental design. In all of the hypertensive patients antihypertensive drug therapy was withheld for at least 1 month before admission to the research ward. All subjects were placed on a constant diet of known electrolyte content for an initial control period of at least 5 days.

The subsequent studies were designed to examine the influence of both potassium depletion and potassium repletion and loading on plasma renin activity. The influence of one or the other of these procedures was examined while sodium

intake was held unchanged from the immediately preceding 5 day control period.

In different studies the effects of either withdrawal or administration of potassium were observed in subjects whose dietary salt was maintained constant at different levels so that the effect of potassium could be observed both during sodium depletion and during maintained sodium administration. In these various studies the constant dietary sodium intake ranged from less than 1 to 269 mEq/day. Constant diets were made up according to the requirements of the studies and the preferences of the subjects. In some studies, both during control and experimental periods, to induce and maintain potassium depletion, a specially prepared nutritionally adequate milk product was employed (product 7000-J, Mead Johnson), which contained 0.04 mEq/100 g of sodium and 0.5 mEq/100 g of potassium. 1 lb. of this powder was given daily together with adequate amounts of corn oil and dextrose. In each study the same basic diet was fed, both during control and experimental periods. In studies involving potassium repletion or potassium loading the additional potassium was given orally in divided doses as the chloride salt in a 20% solution.

Venous blood for the estimation of plasma renin activity was collected at noon after the patients had been ambulatory for at least 4 hr. Control samples were collected on the last day of each control period and frequently during the subsequent experimental periods which lasted from 5 to 13 days. 24-hr urine samples were collected daily during the control and experimental periods and matching days were saved for the determination of aldosterone excretion or secretion rates. The samples collected on the last day of the experimental period were compared to the samples of the control period.

Ward procedures and analytical methods. Metabolism ward techniques and the analytical methods for the measurement of plasma and urine electrolytes and blood urea nitrogen have been reported previously (17). None of the subjects had diarrhea during the studies and stool samples were not saved. Because of this, true over-all electrolyte balance could not be estimated. The changes in renal excretion of sodium and potassium from the control to the experimental periods were used as direct indicators of changes in balance because the kidney is the major route of excretion for sodium and potassium. Accordingly, stool losses of these ions are likely to comprise a small and relatively constant fraction of the total intake, when changes between the control and experimental periods are compared. The urinary excretion rate of these ions for the last day of the control period was compared with the mean excretion rate observed during the experimental periods.

Plasma renin activity was determined by a method previously described (18). With this method, plasma renin activity, when measured at noon in ambient normal subjects on a daily sodium intake of 80–120 mEq, ranges from 0.5 to 2.0 ng/ml per hr. The reproducibility of this method as reported is $\pm 14\%$ (SD). 24-hr aldosterone secretory rates or excretory rates were measured by a double-isotope dilution method, also previously described (19). In normal subjects on a daily sodium intake of 60–120 mEq, mean normal aldosterone excretion is 19.8 $\mu\text{g}/24$ hr. The normal range for aldosterone secretory rates is approximately 10 times that for excretory rates.

Renin substrate was determined by adding an excess of human renin to 0.1 ml of plasma and measuring the amount of angiotensin generated during a 1 hr incubation at 37°C. Renin substrate was measured in 18 studies and was found

to be 1082 ± 337 ng/ml (mean \pm SD) before and 1099 ± 314 ng/ml after potassium administration.

The influence of the potassium ion on the velocity of the renin reaction was determined by incubating pooled plasma to which potassium chloride had been added (4–150 mmoles/liter). No significant differences were observed in the amount of angiotensin generated when these samples were compared to control samples to which no potassium chloride had been added.

RESULTS

Effects of potassium administration. 16 studies in 10 normal subjects and 12 studies in 11 hypertensive patients were carried out. In 18 of these studies potassium administration produced a reduction in plasma renin activity. The mean decrease from the control values was 44%. However, in 10 studies (eight in normals and two in a patient with essential hypertension) plasma renin activity was not suppressed by potassium administration.

Fig. 1 presents the details of a representative study taken from the group of normal subjects. Potassium administration produced a serial and progressive reduction in plasma renin activity. It also induced a slight sodium diuresis at the beginning of the experimental period. Aldosterone secretion was concurrently increased. The serial suppression of plasma renin activity thus occurred in the face of an induced natriuresis, a change which actually would be expected to stimulate plasma renin activity.

Table I includes all studies involving potassium administration in the 10 normal subjects. The results are grouped according to the nature of the stimulus. The first six studies involve potassium repletion of a potassium-depleted state. The eight following studies include potassium loading after a normal potassium intake and the last two studies potassium loading of a potassium-depleted state.

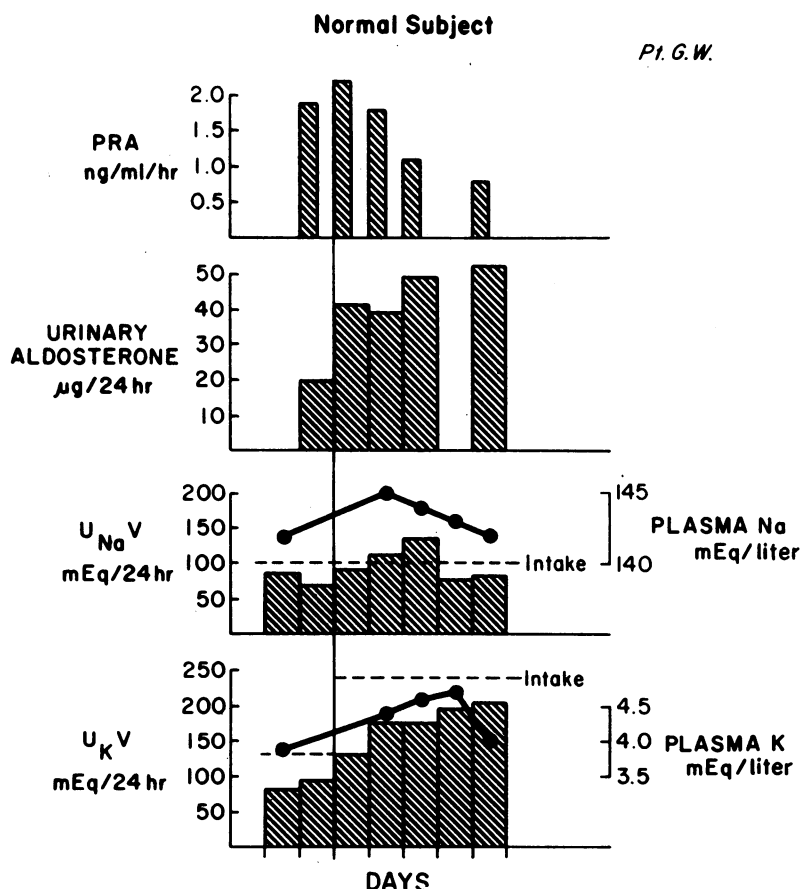


FIGURE 1 Details of a typical study of the effect of potassium administration in a normal subject maintained on a constant dietary regimen. Plasma renin activity was serially suppressed as urinary aldosterone and urinary sodium and potassium increased.

TABLE I
Effect of Potassium Administration on Plasma Renin Activity in Normal Subjects

| Stimulus | Subjects | Mean daily intake | | | Exptl. period | U _{Na} V | | U _K V | | Plasma K ⁺ | | PRA | | Aldosterone | |
|------------------|-----------|-------------------|--------------------|--------------------|---------------|-------------------|-------|------------------|-------|-----------------------|-----|-----------------|------|-----------------|-------|
| | | Na ⁺ | K ⁺ (C) | K ⁺ (E) | | (C) | (E)* | (C) | (E) | (C) | (E) | (C) | (E) | (C) | (E) |
| | | <i>mEq</i> | | | <i>days</i> | <i>mEq/24 hr</i> | | <i>mEq/24 hr</i> | | <i>mEq/liter</i> | | <i>ng/ml/hr</i> | | <i>μg/24 hr</i> | |
| Low potassium | P. K. (2) | 1.7 | 4.1 | 84.6 | 5 | <1 | 7 | 14 | 59.9 | 3.6 | 3.5 | 10 | 6 | 27e | 69e |
| Potassium | J. S. (2) | 121 | 3 | 83 | 7 | 116.5 | 136.5 | 11.0 | 70.7 | 3.1 | 3.8 | 1.5 | 1.5 | 62s | 229s |
| repletion | T. B. (2) | 121 | 3 | 80 | 7 | 105 | 145 | 11.9 | 77.9 | 3.2 | 3.8 | 0.6 | 1.2 | 45s | 232s |
| | G. R. (1) | 0.52 | 0.45 | 81 | 5 | 5.2 | 8 | 14.9 | 77.6 | 3.6 | 3.6 | 7 | 11 | 22e | 38e |
| | J. S. (1) | 1.4 | 3 | 83 | 8 | <1 | 2.8 | 7.8 | 28.5 | 3.5 | 3.6 | 2.4 | 14.1 | 279s | 524s |
| | T. B. (1) | 1.4 | 3 | 83 | 8 | <1 | 11 | 5.7 | 56.2 | 3.7 | 4.2 | 2.7 | 31.2 | 274s | 732s |
| Normal potassium | W. M. | 12.5 | 73.4 | 161 | 5 | <1 | <1 | 66 | 206.4 | 3.3 | 4.8 | 19 | 6.3 | 472s | 783s |
| Potassium | W. G. | 15.3 | 98 | 196.3 | 6 | 4 | 9 | 93.6 | 155.9 | 4.4 | 4.8 | 4.5 | 265s | 975s | |
| loading | M. H. | 13.5 | 126.5 | 214 | 5 | <1 | <1 | 104.7 | 206 | 3.7 | 5.2 | 21.5 | 16 | 1707s | 1221s |
| | D. G. | 13.7 | 130 | 217 | 5 | <1 | <1 | 154.5 | 230.8 | 3.2 | 5.1 | 23.5 | 11 | 701s | 829s |
| | G. W. | 102 | 132 | 239 | 5 | 70 | 100 | 93.2 | 202 | 3.9 | 4.0 | 1.9 | 0.8 | 20e | 52e |
| | R. H. | 118 | 120 | 259 | 13 | 55 | 58 | 57.4 | 261 | 4.0 | | 5 | 1.8 | 140s | 322s |
| | G. R. (2) | 0.52 | 81 | 162 | 5 | 14.3 | 19 | 77.6 | 139 | 3.6 | 4.1 | 11 | 11.5 | 38e | 74e |
| | P. K. (3) | 1.7 | 84.6 | 165 | 5 | 9.7 | 4.6 | 59.9 | 139 | 3.5 | 4.0 | 6 | 8.5 | 69e | 102e |
| Low potassium | P. K. (1) | 173 | 4.1 | 165 | 5 | 110 | 246 | 12.7 | 156 | 2.8 | 3.7 | 1.2 | 0.8 | 2.7e | 20.3e |
| Potassium | G. R. (3) | 171.5 | 0.45 | 161 | 5 | 127 | 238 | 18.6 | 109.7 | 3.3 | 3.8 | 0.7 | 3.6 | 2.3e | 11.8e |
| loading | | | | | | | | | | | | | | | |

s = secretion rate; e = excretion rate; (C) = control period (last day); (E) = experimental period (last day).

* Mean value of experimental period.

Plasma renin activity was suppressed in seven of the ten potassium-loading studies, but only in one of the repletion studies. The suppression of plasma renin activity occurred with either an unchanged or an apparently negative sodium balance. Potassium administration always produced an initial natriuresis. The amounts of sodium lost were not substantially different whether or not plasma renin activity was suppressed. Aldo-

sterone secretion was stimulated in all but one of the 16 studies. The increase in aldosterone excretion was consistent despite a very inconsistent response of renin.

Table II presents the results of 12 studies involving potassium administration in 11 hypertensive patients. The results were essentially the same as those obtained in the normal subjects. In 10 studies plasma renin activity was suppressed by potassium administration.

TABLE II
Effect of Potassium Administration on Plasma Renin Activity in Hypertensive Patients

| Stimulus | Patients and diagnoses | Mean daily intake | | | Exptl. period | U _{Na} V | | U _K V | | Plasma K ⁺ | | PRA | | Aldosterone | |
|------------------|------------------------|-------------------|--------------------|--------------------|---------------|-------------------|------|------------------|-------|-----------------------|-----|-----------------|-------|-----------------|-------|
| | | Na ⁺ | K ⁺ (C) | K ⁺ (E) | | (C) | (E)* | (C) | (E) | (C) | (E) | (C) | (E) | (C) | (E) |
| | | <i>mEq</i> | | | <i>days</i> | <i>mEq/24 hr</i> | | <i>mEq/24 hr</i> | | <i>mEq/liter</i> | | <i>ng/ml/hr</i> | | <i>μg/24 hr</i> | |
| Low potassium | M. G. (1) EH | 103 | 0.36 | 81 | 4 | 95† | 106 | 11.6 | 38.4 | 3.0 | 3.6 | 5.2 | 5.6 | 74s | 250s |
| Potassium | | | | | | | | | | | | | | | |
| repletion | | | | | | | | | | | | | | | |
| Normal potassium | E. Gu. EH | 93 | 68 | 158 | 6 | 66 | 78 | 62.8 | 84.6 | 4.0 | 5.0 | 16 | 6.5 | 44e | 110e |
| Potassium | A. T. RH | 95 | 76 | 183 | 5 | 78 | 96 | 80.9 | 216.6 | 3.1 | 4.2 | 4.4 | 3.3 | 575s | 1040s |
| loading | M. E. EH | 96.4 | 95 | 203 | 5 | 76.3 | 100 | 72.2 | 183.9 | 3.7 | 4.0 | 1.0 | 0.6 | 191s | 219s |
| | A. H. EH | 97 | 62 | 175 | 5 | 73 | 90 | 34 | 128 | 3.8 | 4.5 | 4.5 | 1.8 | 107s | 570s |
| | M. A. RH | nl‡ | nl‡ | nl +140‡ | 9 | 80.9 | 63 | 74.5 | 180 | 2.4 | 3.6 | 76.5 | 38.5 | 464s | 1587s |
| | J. R. RH | nl‡ | nl‡ | nl +80‡ | 6 | 53 | 80.5 | 75 | 108.3 | | | 276.5 | 201.5 | 38e | 78e |
| | E. Gr. EH | lo‡ | nl‡ | nl +80‡ | 5 | <1 | 4 | 50.2 | 61.1 | 3.8 | 4.0 | 6.4 | 1.5 | | |
| | L. G. EH | 269 | 81 | 159 | 6 | 220 | 300 | 61.5 | 149.8 | 3.5 | 4.3 | 1.1 | 0.6 | 85s | 90s |
| Low potassium | M. S. EH | 1.04 | 1 | 162 | 5 | <1 | 8.7 | 5.1 | 141 | 3.3 | 4.2 | 11 | 7.5 | 621s | 1465s |
| Potassium | A. P. EH | 1.6 | 4 | 165 | 5 | <1 | 7 | 15.1 | 161.2 | 4.3 | 4.9 | 4.6 | 3.2 | | |
| loading | M. G. (2) EH | 0.26 | 0.36 | 162 | 7 | <1 | 19 | 7.8 | 132 | 3.0 | 3.8 | 7.5 | 8.3 | 234s | 1001s |

s = secretion rate; e = excretion rate; EH = essential hypertension; RH = renovascular hypertension; (C) = control period (last day); (E) = experimental period (last day).

* Mean value of experimental period.

† Mean value of 3 days.

‡ Constant hospital diet with either low or normal sodium content and normal potassium content.

Fig. 2 summarizes the effect of potassium administration on plasma renin activity and aldosterone secretion or excretion in normal subjects and in hypertensive patients. It is apparent that potassium loading almost always suppressed plasma renin activity, where potassium repletion failed to suppress plasma renin activity in six of seven studies.

Effect of potassium depletion. In six studies of two normal subjects and three patients with essential hypertension, potassium depletion invariably produced an increase in plasma renin activity. Associated with the in-

creased plasma renin activity, a decrease in urinary aldosterone excretion was observed in four of the five studies in which it was measured. The stimulation of plasma renin activity by potassium depletion occurred despite a slight tendency to sodium retention observed in all six of these studies. These results are presented in Table III and in Fig. 3.

Relationship between plasma renin and the changes in plasma potassium and urinary potassium excretion. An attempt was made to correlate the observed changes in plasma renin activity with the concurrently induced

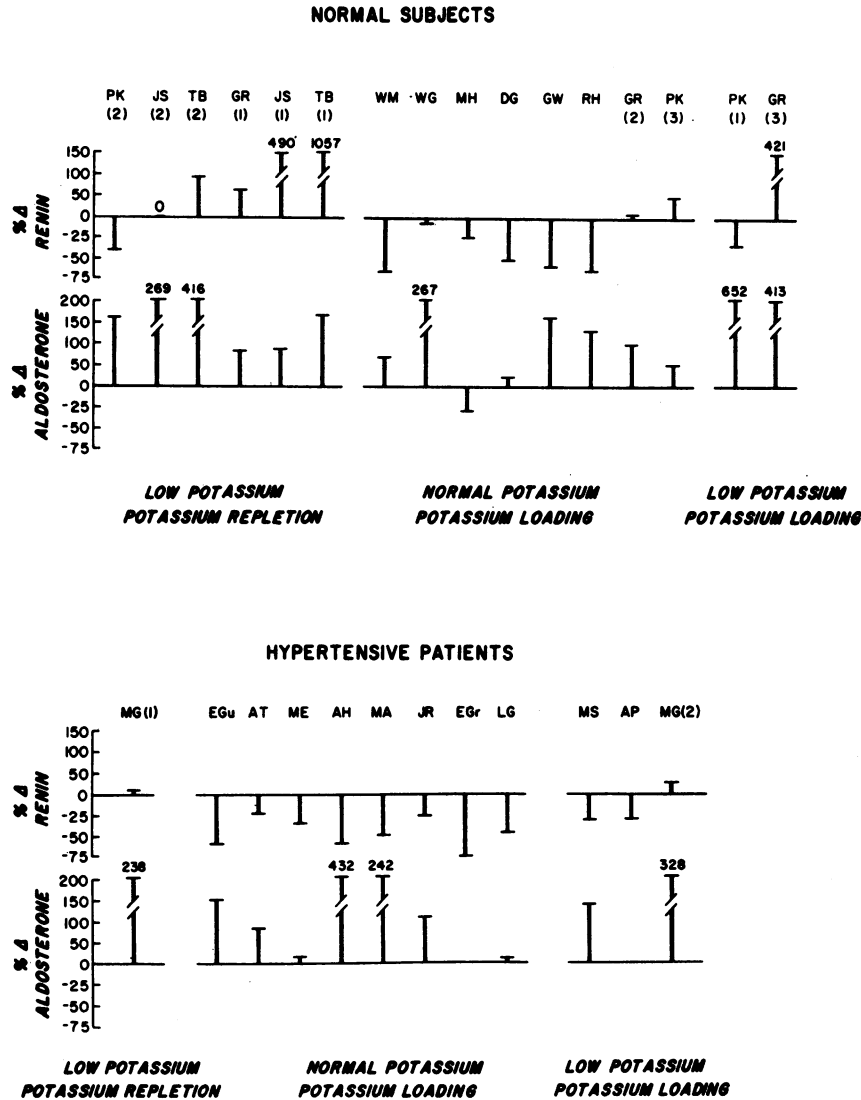


FIGURE 2 The effect of potassium administration on plasma renin activity and aldosterone secretion or excretion in normal subjects and in hypertensive patients is summarized. Potassium loading almost always suppressed plasma renin activity, where potassium repletion failed to suppress plasma renin activity in six of the seven studies. Aldosterone secretion was stimulated in 25 of 26 studies.

TABLE III
Effect of Potassium Depletion on Plasma Renin Activity in Normal Subjects and in Hypertensive Patients

| Stimulus | Subjects | | Mean daily intake | | | Exptl. period | U _{Na} V | | U _K V | | Plasma K ⁺ | | PRA | | Aldosterone | |
|--|-----------|----|-------------------|--------------------|--------------------|------------------|-------------------|------|------------------|------|-----------------------|-----|-----------------|-----|-----------------|-------|
| | | | Na ⁺ | K ⁺ (C) | K ⁺ (E) | | (C) | (E)* | (C) | (E) | (C) | (E) | (C) | (E) | (C) | (E) |
| | | | <i>mEq</i> | | <i>days</i> | | <i>mEq/24 hr</i> | | <i>mEq/24 hr</i> | | <i>mEq/liter</i> | | <i>ng/ml/hr</i> | | <i>μg/24 hr</i> | |
| Normal potassium Potassium depletion | M. S. | EH | 1.04 | 82 | 0.97 | 6 | 15 | 1 | 61.5 | 5.1 | 4.6 | 3.3 | 7.5 | 11 | 677s | 621s |
| | A. P. (1) | EH | 1.6 | 84 | 4 | 5 | 25.7 | 2.6 | 68.6 | 15.1 | 3.9 | 4.3 | 3.7 | 4.6 | 315s | 280s |
| | E. W. | EH | 1.7 | 84.6 | 4.1 | 5 | 10 | 2 | 80.1 | 20.4 | 4.7 | 4.4 | 13 | 30 | 681s | 732s |
| High potassium Potassium depletion | G. R. | NS | 0.52 | 162 | 0.45 | 5 | 9.2 | 1 | 139 | 26.4 | 4.1 | 4.0 | 11.5 | 15 | 74e | 58e |
| | P. K. | NS | 1.7 | 165 | 4.1 | 5 | 3.2 | 1 | 139 | 17.7 | 4.0 | 3.8 | 8.5 | 10 | 102e | 61.4e |
| | A. P. (2) | EH | 1.6 | 165 | 4 | 5 | 8.9 | <1 | 161.2 | 16.9 | 4.9 | 3.7 | 3.2 | 5.5 | | |

s = secretion rate; e = excretion rate; (C) = control period (last day); (E) = experimental period (last day); NS normal subject; EH essential hypertension.

* Mean value of experimental period.

changes in plasma potassium concentrations and in the rates of urinary potassium excretion (U_KV). Fig. 4 summarizes these relationships. Data from all studies are plotted. It is apparent that a gross inverse relationship obtains between the changes induced in plasma potassium and/or urinary potassium excretion and the associated changes induced in plasma renin activity. That this relationship does not always hold is illustrated by the points derived from the 10 studies shown by open circles, in which potassium administration failed to suppress plasma renin values (group II).

One reason for the failure of potassium administration to suppress plasma renin in these 10 of the 28 studies is suggested by data presented in Table IV. These data indicate that, on an average, the group II patients received lesser amounts of potassium ($P < 0.001$) and they

consequently achieved relatively lower levels of plasma potassium concentration ($P < 0.01$) and lower rates of urinary potassium excretion ($P < 0.01$) during potassium administration than did those subjects whose plasma renin activity was suppressed (group I). It therefore seems likely that the failure of potassium loading to suppress renin in group II subjects can be explained at least in part by the differences in the amounts of potassium which were administered. That a certain critical amount of potassium must be given in order to consistently induce suppression of plasma renin is also suggested by the plot of the data from all of the individual studies (Fig. 4). It appears here that whenever plasma potassium levels were increased by more than 25% or whenever U_KV exceeded 100 mEq/day significant suppression of plasma renin was practically always produced.

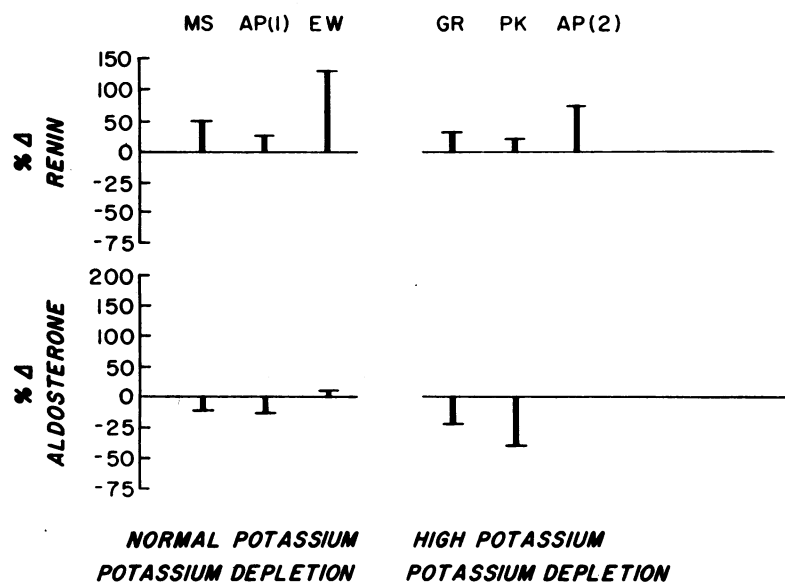


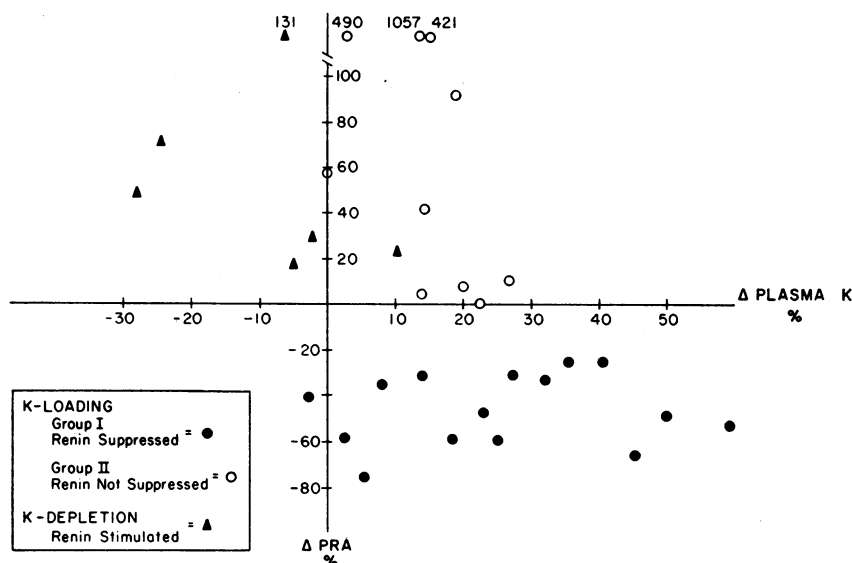
FIGURE 3 In six studies, potassium deprivation consistently induced increases in plasma renin activity. Aldosterone excretion was usually reduced.

With the opposite influence (i.e., potassium depletion), a much more uniform response pattern was observed. Even when potassium depletion did not appreciably reduce the plasma potassium value, plasma renin activity was nonetheless significantly stimulated.

DISCUSSION

These studies demonstrate that potassium loading can suppress plasma renin activity in normal subjects and in patients with essential or with renovascular hypertension. These results confirm and extend the observations of

RELATIONSHIP BETWEEN CHANGE IN PLASMA POTASSIUM CONCENTRATION & CHANGES INDUCED IN PLASMA RENIN ACTIVITY DURING POTASSIUM-LOADING OR POTASSIUM-DEPLETION



RELATIONSHIP BETWEEN CHANGES IN $U_{K/V}$ & CHANGES INDUCED IN PLASMA RENIN ACTIVITY DURING POTASSIUM-LOADING OR POTASSIUM-DEPLETION

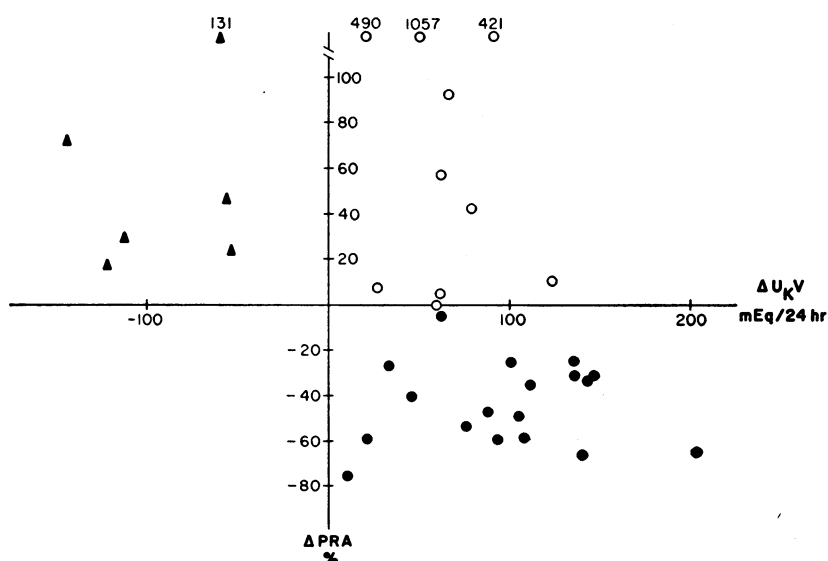


FIGURE 4 Changes induced in plasma renin activity are plotted on the ordinates against concurrently induced changes in plasma potassium concentration and urinary potassium excretion. Data from all of the studies involving potassium administration or deprivation are included.

TABLE IV
Relationship of Plasma Renin Activity to Potassium Intake, to U_KV , and Plasma Potassium Concentration after Potassium Administration

| | Δ PRA | Potassium-intake | U_KV^* | Plasma-potassium* |
|------------------------------------|-------------------|------------------|------------------|-------------------|
| | % | mEq/24 hr | mEq/24 hr | mEq/liter |
| Renin suppressed (group I) | -43.5 ± 4.3 | 182.7 ± 10.7 | 160.7 ± 13.4 | 4.3 ± 0.1 |
| Renin not suppressed (group II) | 218.1 ± 109.1 | 114.1 ± 13.1 | 87.3 ± 13.8 | 3.8 ± 0.1 |
| Significance level | | $P < 0.001$ | $P < 0.01$ | $P < 0.01$ |

Results = mean \pm SE.

* Measured the last day of the experimental period.

Veyrat, Brunner, Manning, and Muller (14) who produced renin suppression by potassium loading in normal subjects maintained on low sodium diets. Suppression of plasma renin activity by potassium loading has been noted by Maebashi, Miura, and Yoshinaga (20) in patients with renovascular hypertension and it has also been described in acute experiments in dogs involving potassium infusions (15, 16).

In our studies as well as in the reported animal experiments, potassium loading usually induced a transient sodium loss. This was not described in the human studies by either Veyrat or Maebashi and their coworkers (14, 20). This sodium loss would be expected to cause an increase in plasma renin. Even so, in our studies plasma renin activity was most often suppressed by potassium administration. Therefore, potassium administration can induce a lowering of plasma renin activity, even in the presence of a concurrently induced sodium diuresis. This suppression of renin was found to be directly related to, but not always closely correlated with, the changes induced in both plasma potassium and the rate of urinary potassium excretion (Fig. 4).

The 10 studies (group II) in which the administration of potassium salt was not associated with any suppression of plasma renin, indicate that this effect is not a consistent one. These results suggest, that there are certain specific requirements for the influence of potassium on plasma renin to occur. There are several reasons which might explain the failure of renin suppression to occur in these 10 studies (group II). First of all the subjects in this group received smaller amounts of potassium and accordingly, lesser increases in plasma potassium concentration and in urinary potassium excretion were produced, when compared with corresponding values for the subjects included in group I. These three quantitative differences were highly significant (Table IV). It is of note that even though the subjects of group II received less potassium salt than did subjects of group I the natriureses induced by this treatment were

of the same general order of magnitude for the two groups. It seems possible therefore, that a commensurate natriuresis induced in the subjects of group II by the smaller amounts of potassium given might have been able to exert an overriding and stimulatory effect on plasma renin, as evidenced by the increases in renin actually observed in 9 of the 10 studies of this group. Possibly, when larger amounts of potassium are given, its renin-suppressing influence then supervenes, even in the face of the simultaneous stimulating influence of an induced sodium loss. In other words, in an individual situation, whether or not renin will be suppressed by potassium ions, will depend in part, on the relative strength of an opposing renin-stimulating influence, i.e., sodium depletion. It is also possible that by chance, more of the subjects included in group II were susceptible to further sodium depletion. In this regard, it should be appreciated, that despite careful attention to standardized conditions, certain subjects undoubtedly lose more sodium than do others in going into balance on a low sodium diet. These subjects may be especially vulnerable to any further sodium loss induced in the case of the present studies by potassium.

The nature of the role of changes in potassium metabolism in the regulation of renin secretion is further clarified by studies involving dietary potassium depletion. This procedure always produced an increase in plasma renin activity in both normal and hypertensive subjects. These increases in plasma renin activity often occurred despite a concurrent tendency towards renal sodium retention, an influence which per se would be expected to suppress plasma renin activity. All studies involving potassium depletion were carried out on a low sodium diet. It is possible that on a normal salt intake some overriding effect of changes in sodium balance would also have appeared. These observations on the stimulating effect of potassium depletion complement the loading experiments which define a capacity for potassium administration to suppress plasma renin ac-

tivity. As indicated, neither effect can be explained in terms of any concurrently induced change in sodium balance. Taken together, the results of the present studies therefore suggest a broad role for potassium ions in the regulation of plasma renin activity.

The mechanisms by which changes in potassium metabolism affect plasma renin activity remain to be fully clarified. It seems quite unlikely that the changes observed were induced by an associated change in aldosterone secretion. It is true that in 25 of 26 studies potassium administration increased aldosterone excretion. However, aldosterone excretion was increased to the same extent whether (group I) or not (group II) plasma renin was suppressed. Furthermore, there is a large body of evidence to indicate that aldosterone or other mineralocorticoids do not, by themselves, suppress plasma renin because the suppression produced by these hormones was found to be entirely consequent to induced sodium retention (21–23).

Changes in potassium balance might conceivably change plasma renin activity by interfering with the degradation processes involved in metabolizing renin. This possibility seems unlikely because one might reasonably expect any interference with the metabolism of renin to be reflected in an appropriate compensation in renal renin secretion. Other possible mechanisms are a direct inhibiting effect of plasma potassium concentration on the enzyme renin or an effect of potassium administration on renin substrate concentration. However, as described above, studies in our laboratory have failed to demonstrate either of these effects (24). Changes in potassium metabolism might also operate to induce the release of an extrarenal hormone concerned with the control of renal renin secretion. But there is little evidence to support such a mechanism.

At present, it seems most likely that changes in potassium metabolism influence plasma renin activity by a direct intrarenal effect on renin secretion. This interpretation is supported by acute infusion (15), and renal perfusion studies (15, 16) in which renal renin secretion was reduced by potassium ions. An intrarenal mechanism is also supported by the present longer-term studies, because possible extrarenal mechanisms seem unlikely and because both the renin-suppressing effect of potassium administration and the renin-stimulating effect of potassium deprivation could be related to associated changes in plasma potassium levels and urinary potassium excretion.

Potassium ions could affect renal renin secretion by modifying intrarenal hemodynamics. No significant or consistent influences on glomerular filtration rate or renal plasma flow have been reported following administration of potassium salts in amounts of the same

order of magnitude used in the present studies. On the other hand, potassium depletion has been reported to reduce GFR and RPF (25) and acute hypokalemia has been noted to increase renal resistance (26). However, much more drastic or prolonged potassium depletion than that applied in the present studies was required to produce these changes. The possibility also remains that changes in available potassium ions could modify the intrarenal distribution of blood flow but there is no evidence now available on this point.

A direct influence of changes in plasma potassium concentration on a specific sensor perhaps in the juxtaglomerular or in the macula densa cells is not excluded by the present observations. A change in tubular transport of potassium might also be a signal. Available data are scant but they suggest that most of the filtered potassium is reabsorbed at sites proximal to the macula densa (27, 28) so that a change in tubular fluid $[K^+]$ seems an unlikely signal. An increase in the rate of transtubular secretion of potassium might also have a direct effect on renal renin secretion. However, tubular secretion of potassium is thought to occur at a site beyond the macula densa region (27).

Finally, potassium ions might affect renal renin secretion by inducing intrarenal changes in sodium transport which could modify the amount or the concentration of sodium ions presented to the macula densa. In this context potassium depletion has been reported to increase proximal tubular sodium reabsorption (29, 30), an effect which would reduce the amount of sodium delivered to a sensor at the macula densa and thereby perhaps stimulate renin release. In addition, potassium depletion has been shown to reduce GFR (29, 30) which might also reduce the sodium load delivered to the macula densa.

There are no data available on the effect of potassium loading on proximal tubular reabsorption. However, because this procedure often produces transient natriuresis, an increased sodium delivery to the macula densa might be involved, at least initially, in the renin suppression. Such a mechanism may not adequately explain the chronic suppression of renin caused by potassium loading, because this can obtain even after sodium depletion is established, at a time when the rate of urinary sodium excretion is very low (14, 24).

There are a number of clinical situations which can be explained in the context of the present observations. For example, we have observed a number of potassium-depleted patients due to anorexia nervosa, ulcerative colitis, or excessive laxative usage, all of whom have exhibited extremely high plasma renin values, even after sodium repletion. Indeed, such clinical observations encouraged us to undertake the studies described herein.

Patients with primary aldosteronism might appear at first to present a situation which cannot be explained in terms of the present observations. These patients exhibit very low plasma renin levels in the presence of potassium depletion. However, in this condition it is likely that the influence of a positive sodium balance predominates and suppresses renin by overriding the stimulatory influence of potassium depletion. In other situations, such as in our group II subjects sodium stimulus also seems to predominate. In this group the stimulus to increased renin secretion of sodium depletion supervenes over the suppressing influence of potassium. On the other hand, in primary juxtaglomerular cell hyperplasia (Bartter's syndrome) the plasma renin levels are enormously increased, even after sodium repletion (31), suggesting that in this particular situation, potassium depletion is the more dominant signal.

Further work is required to fully define the nature of the influence of potassium ions on the renin-angiotensin-aldosterone hormonal system. However, the present studies point up a new dimension in this hormonal interaction. It now appears that changes in available potassium ions can operate simultaneously to regulate both adrenal cortical aldosterone secretion and renal renin secretion. Also, it is now apparent that depletion of either sodium or potassium ions will activate renal renin secretion. However, in the former instance, aldosterone secretion is stimulated whereas in the latter it is curtailed. Sodium conservation in the presence of potassium depletion does not seem to require increased aldosterone action, perhaps because the potassium depletion may increase renal tubular sodium transport by other means (29, 30, 32). Whatever the interactions finally prove to be, it is clear that the renin-angiotensin system is organized to simultaneously regulate sodium, potassium, and blood pressure homeostasis.

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